Narcolepsy type 2: A rare, yet existing entity

Baumann-Vogel, Heide ; Schreckenbauer, Lina ; Valko, Philipp O ; Werth, Esther ; Baumann, Christian R

Abstract: Because of unspecific diagnostic criteria, there is much controversy around narcolepsy type 2, its existence and its frequency. With this retrospective and purely descriptive study, we aimed to compare the frequency of narcolepsy type 2 compared to the well-described narcolepsy type 1, in a large (n = 3,782) retrospective sample from a single tertiary sleep centre. After 2 weeks washout of sleep-wake active medication, all patients with excessive daytime sleepiness (n = 1,392) underwent 2 weeks actigraphy, polysomnography and multiple sleep latency test, and all diagnoses were made along current diagnostic criteria. Narcolepsy type 1 was diagnosed in 91 patients, and 191 patients without cataplexy had multiple sleep latency test (MSLT) results indicating narcolepsy. After exclusion of shift work syndrome (n = 19), suspected insufficient sleep syndrome (n = 128), delayed sleep phase syndrome (n = 4) and obstructive sleep apnea (n = 34), six patients were diagnosed with narcolepsy type 2, of whom two patients later developed narcolepsy type 1. Altogether, our observations suggest that narcolepsy type 2 exists, but its frequency may be much lower compared to narcolepsy type 1. In addition, they emphasize the importance of scrupulously excluding other potential causes of sleepiness, if possible, with 2-week actigraphy and polysomnography.

DOI: https://doi.org/10.1111/jsr.13203

Zurich, August 30, 2020

Narcolepsy type 2: a rare, yet existing entity

Heide Baumann-Vogel, MD, Lina Schreckenbauer,

Philipp O. Valko, MD, Esther Werth, PhD, Christian R. Baumann, MD

Department of Neurology
University Hospital Zurich
University of Zurich
Frauenklinikstrasse 26
8091 Zurich
Switzerland

All authors have seen and approved the manuscript.

No co-author has received financial support for this work.

No author declares a conflict of interest defined as any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated.

Number of tables	1
Number of figures	1
Word count (summary, keywords, main body)	1982
References	15

Corresponding author:

Christian R. Baumann, Department of Neurology, University Hospital Zurich, University of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland – christian.baumann@usz.ch – Phone +41 44 255 5502

Summary

Because of unspecific diagnostic criteria, there is much controversy around narcolepsy type 2, its existence and its frequency. With this retrospective and purely descriptive study, we aimed to compare the frequency of narcolepsy type 2 compared to the well-described narcolepsy type 1, in a large (n=3782) retrospective sample from a single tertiary sleep center. After 2 weeks wash-out of sleep-wake active medication, all patients with excessive daytime sleepiness (n=1392) underwent 2 weeks actigraphy, polysomnography, and multiple sleep latency test, and all diagnoses were made along current diagnostic criteria. Narcolepsy type 1 was diagnosed in 91 patients, and 191 patients without cataplexy had MSLT results indicating narcolepsy. After exclusion of shift work syndrome (n=19), suspected insufficient sleep syndrome (n=128), delayed sleep phase syndrome (n=4), and obstructive sleep apnea (n=34), 6 patients were diagnosed with narcolepsy type 2, whereof 2 patients later developed narcolepsy type 1. Altogether, our observations suggest that narcolepsy type 2 exists, but its frequency may be much lower compared to narcolepsy type 1. In addition, they emphasize the importance of scrupulously excluding other potential causes of sleepiness, if possible with 2-week actigraphy and polysomnography.

Keywords: narcolepsy, hypersomnia, excessive daytime sleepiness, shift work, insufficient sleep syndrome, delayed sleep phase syndrome

Introduction

Narcolepsy type 1 is a very well defined disorder, caused by an almost total loss of hypothalamic hypocretin (orexin) levels. It presents with sleepiness, cataplexy, fragmented nocturnal sleep, and other associated symptoms such as sleep paralysis and hypnagogic/hypnopompic hallucinations (AASM, 2014; Bassetti, 2019). This form of narcolepsy is diagnosed in sleepy patients with pathologically reduced cerebrospinal fluid hypocretin (orexin) levels or when typical multiple sleep latency tests (MSLT) findings are accompanied by pathognomonic cataplexy (AASM, 2014). The prevalence is around 2-5 per 10'000 individuals (Bassetti, 2019).

On the other hand, narcolepsy type 2 is much more difficult to diagnose (Baumann, 2014; Bassetti, 2019). It lacks pathognomonic symptoms such as cataplexy, and cerebrospinal fluid levels are normal, if measured. Thus, the current diagnostic criteria require chronic excessive daytime sleepiness, absent cataplexy, typical MSLT findings with a mean sleep latency below 8 minutes and at least 2 sleep onset REM periods, whereof a polysomnography sleep onset REM (defined as REM onset latency ≤15 min) can be counted as well. In addition, the criteria require that the symptoms shall not be "better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal" (AASM, 2014).

Due to the lack of specific criteria and biomarkers, narcolepsy type 2 is still widely debated. It remains unclear whether narcolepsy type 2 is more, equally, or less frequent than narcolepsy type 1. In addition, there is an ongoing debate whether narcolepsy type 2 is merely a transient diagnosis until cataplexy - i.e. narcolepsy type 1 – emerges (Goldbart, 2014; Baumann, 2014). The observation of a poor test-retest reliability of the MSLT particularly in narcolepsy type 2 adds to diagnostic uncertainty

(Trotti, 2013; Ruoff, 2018). In particular, it has been shown that chronic sleep restriction and shift work often produce narcolepsy-like MSLT findings (Marti, 2009; Goldbart, 2014).

In a cross-sectional laboratory-based analysis in a sample of 539 people, the prevalence of multiple sleep onset REM periods was 3.9%, particularly in patients with a mean sleep latency below 5 minutes (Singh, 2006). Given their findings, the authors concluded that subpopulations with excessive sleepiness including shift workers, young adults with chronic sleep restriction, and patients with sleep apnea, are likely to have a greater prevalence of sleep onset REM. Based on narcolepsy-like MSLT findings in 5.9% of males and 1.1% of females, all without cataplexy, in another community-based cohort of 556 subjects, the authors concluded that narcolepsy type 2 might be highly prevalent, or that MSLT might produce a large number of false-positive results (Mignot, 2006). In this study, however, shift work syndrome and chronic sleep restriction were not systematically excluded. In the same cohort, a later study aimed to exclude patients with shift work syndrome and short sleep and still found a 3-fold larger prevalence of narcolepsy type 2 compared to type 1 (Goldbart, 2014). Nevertheless, actigraphy measures were not available in this study.

Thus, we aimed to compare the frequencies of both types of narcolepsy in a large retrospective single-center cohort, which has been examined with actigraphy, polysomnography, and MSLT.

Methods

Within this study that has been approved by the local ethical committee, we analyzed 3782 patients who have been examined with polysomnography in the sleep laboratory of the neurology department in our hospital between fall 2002 and early 2020, and

applied the current diagnostic criteria to all patients (AASM, 2014). Prior to sleep laboratory examinations, all patients with chronic excessive daytime sleepiness were washed out for 2 weeks of CNS active medications which might cause or contribute to excessive daytime sleepiness or to altered sleep laboratory findings. In addition, all patients underwent extensive history-taking and a neurological examination in the outpatient unit, and filled out a set of standardized questionnaires (including the Epworth sleepiness scale, Fatigue severity scale, Hospital Anxiety and Depression Scale).

Patients were examined by the means of 2 weeks actigraphy, followed by video-polysomnography and an MSLT, as described before (Imbach, 2015). In patients with narcolepsy-like MSLT who did not qualify for narcolepsy type 1, we required the exclusion of disorders that can produce such MSLT findings. In particular, we strived for excluding insufficient sleep syndrome and shift work syndrome which both may present with narcolepsy-like MSLT findings (Marti et al., 2009; Mignot, 2006), but also for excluding sleep apnea and circadian sleep-wake disorders (AASM, 2014; Bassetti, 2019). In patients with excessive daytime sleepiness who had a pathological MSLT with low mean sleep latency (< 8 minutes) and multiple sleep onset REM periods, and who slept at least 2 hours more during weekends, we evaluated by history-taking whether sleepiness was relieved in times without work, e.g during holidays or during unemployement. In patients who fulfilled all these requirements and therefore in line with the current diagnostic criteria, we diagnosed suspected insufficient sleep syndrome (AASM 2014, Baumann-Vogel 2020). Excessive daytime sleepiness due to shift work syndrome was diagnosed based on history, actigraphy and MSLT findings, as suggested by the current diagnostic criteria (AASM, 2014). In sleepy patients with increased sleep need (at least 11 hours per 24 hours) and/or sleep inertia, we suspected idiopathic hypersomnia (AASM, 2014; Baumann, 2014). For the diagnosis

of obstructive sleep apnea, and again in accordance with the current diagnostic criteria, we required an apnea-hypopnea index of at least 5 on polysomnography in patients with EDS and a history of nocturnal awakenings with breath holding, gasping, choking and observations of habitual snoring and/or breathing interruptions by bedpartners (AASM, 2014).

Results

Among 1392 patients with excessive daytime sleepiness (as defined by an Epworth sleepiness scale value of at least 11 points) and without significant neurological or psychiatric comorbidities, we identified 91 patients with narcolepsy type 1 (2.4% of the examined population), all of them with typical MSLT findings (Figure 1). In addition, we found the combination of a mean sleep latency <8 minutes plus multiple sleep onset REM periods in another 191 patients (5.1%). Of these, history-taking and actigraphy recordings suggested insufficient sleep syndrome in 128 patients, shift work syndrome in 19 patients, delayed sleep phase syndrome in 4 patients, and 34 patients were diagnosed with obstructive sleep apnea. Two longitudinally followed patients evolved into narcolepsy type 1. In 4 patients without findings hinting at such other disorders, we diagnosed narcolepsy type 2. These four patients are summarized in Table 1, all of them were HLA-DQB1*0602-positive, all of them male. One elderly patient (no 3) developed narcolepsy symptoms after a tick bite.

Discussion

The findings of this study suggest that narcolepsy type 2 exists, but its frequency may be up to 20-25x lower compared to narcolepsy type 1. For the sleep clinician, this

observation shall motivate to scrupulously exclude other potential reasons for narcolepsy-like MSLT findings, particularly shift work and insufficient sleep syndrome, but also circadian disorders and sleep apnea. This is important, as these disorders require markedly different therapies, spanning from non-pharmacological sleep hygiene to stimulants or continuous positive airway pressure treatment. For the sleep scientist, the findings of the present study may provoke a critical reading of reports on narcolepsy type 2, if actigraphy and other tests and parameters have not been used to exclude other causes of sleepiness and enhanced REM sleep pressure.

To achieve a solid diagnosis, objective assessments of rest-activity rhythms with 2-week actigraphy are most likely superior to history taking or sleep logs. Given observations from human studies, the habitual sleep need of young people might be around 9 hours per day, and 7.5 hours in the elderly (Klerman, 2008). Many of us sleep much less, which makes insufficient sleep syndrome most probably a very prevalent phenomenon (Baumann-Vogel et al., 2020). In addition, a sleep stage sequence WAKE→NREM1→REM on MSLT and even more a short REM sleep latency during polysomnography are strong indicators for the presence of narcolepsy and should be considered as well (Andlauer et al., 2013; Marti, 2009).

In a recent opinion statement, some European colleagues addressed the diagnostic challenges around narcolepsy type 2 and proposed to replace “narcolepsy type 1” and “narcolepsy type 2” by “narcolepsy” (Lammers et al., 2020). They suggest to diagnose definite narcolepsy in the presence of excessive daytime sleepiness in combination with hypocretin deficiency and/or typical cataplexy with typical MSLT results. This corresponds to the current diagnostic criteria of narcolepsy type 1 (AASM, 2020). To diagnose probable narcolepsy, their proposed criteria require excessive daytime sleepiness and either (1) typical cataplexy and a sleep latency on MSLT below 8

minutes or multiple sleep onset REM periods, or (2) hypnagogic hallucinations and/or sleep paralysis and/or disturbed nocturnal sleep and an MSLT with an even shorter mean sleep latency (<5 minutes) or with even more (>2) sleep onset REM periods, plus positive HLA DQB1*0602 testing and exclusion of other causes of sleepiness (Lammers, 2020). Although their proposal did not include neither the sequence of sleep stages during MSLT nor sleep onset REM during polysomnography which might have further sharpened the diagnostic criteria, and although such an approach mixes a group of very well-defined patients with a potentially mixed bag of hypersomnia patients, this proposal would at least most likely contribute to lower numbers of false positive narcolepsy diagnoses (Marti et al., 2009; Andlauer, 2014). Whatever the next generation of diagnostic criteria for narcolepsy might look like, given the present and previous findings, such new criteria for narcolepsy without cataplexy or without hypocretin deficiency must put a stronger emphasis on the exclusion of other disorders, and therefore should specifically recommend related examinations (polysomnography, actigraphy).

This retrospective analysis has limitations. First of all, it does not solve the question what narcolepsy type 2 is. Is it a separate disease, a subtype of narcolepsy, a prodromal stage of narcolepsy type 1, or a form of idiopathic hypersomnia with normal night sleep periods and without sleep inertia? Second, we suspected insufficient sleep syndrome along the current diagnostic criteria, but in the majority of patients, we did not prove this diagnosis by extending sleep times which is expensive and burdensome (Baumann-Vogel et al., 2020). On the other hand, we have information from all patients with suspected insufficient sleep syndrome that sleepiness remits or significantly improves during holidays, which is in strong favor of this diagnosis rather than narcolepsy. Third, another limitation concerns the assessments in a preselected referred clinical population. We therefore cannot estimate a population-based

prevalence, but only deduce that narcolepsy type 2 may be much rarer than type 1. Last not least, a fourth limitation is the fact that we do not perform HLA assessments in all sleepy patients, mostly because of the high costs which are not regularly covered by insurance companies. Nevertheless, given the low specificity of positive HLA DQB1*0602 results for narcolepsy, we consider this limitation as minor (Hong, 2006).

Disclosure Statement:

Heide Baumann-Vogel. Financial disclosure: None. Non-financial disclosure: None.

Lina Schreckenbauer: Financial disclosure: None. Non-financial disclosure: None.

Esther Werth: Financial disclosure: None. Non-financial disclosure: None.

Philipp Valko: Financial disclosure: None. Non-financial disclosure: None.

Christian R. Baumann: Financial disclosure: None. Non-financial disclosure: None.

Authorship:

All authors listed on the manuscript have contributed significantly to the collection, analysis and/or interpretation of the data. All authors have read and approved the submitted version.

Acknowledgements:
None.

References

American Academy of Sleep Medicine (AASM) (2014). International Classification of Sleep Disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine.

Andlauer O, Moore H, Jouhier L, et al. Nocturnal rapid eye movement sleep latency for identifying patients with narcolepsy/hypocretin deficiency [published correction appears in JAMA Neurol. 2013 Oct;70(10):1332]. JAMA Neurol. 2013;70(7):891-902.

Bassetti, C., Adamantidis, A., Burdakov, D., Han, F., Gay, S., Kallweit, U., Khatami, R., Koning, F., Kornum, B. R., Lammers, G. J., Liblau, R. S., Luppi, P. H., Mayer, G., Pollmächer, T., Sakurai, T., Sallusto, F., Scammell, T. E., Tafti, M., & Dauvilliers, Y. (2019). Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nature reviews. Neurology, 15(9), 519–539.

Baumann, C. R., Mignot, E., Lammers, G. J., Overeem, S., Arnulf, I., Rye, D., Dauvilliers, Y., Honda, M., Owens, J. A., Plazzi, G., & Scammell, T. E. (2014). Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. Sleep, 37(6), 1035–1042.

Baumann-Vogel H, Hoff S, Valko PO, Poryazova R, Werth E, Baumann CR. Extending sleep to confirm insufficient sleep syndrome is challenging [published online ahead of print, 2020 Jun 18]. J Sleep Res. 2020;e13109.

Goldbart, A., Peppard, P., Finn, L., Ruoff, C. M., Barnet, J., Young, T., & Mignot, E. (2014). Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. Sleep, 37(6), 1043–1051.

Hong, S. C., Lin, L., Jeong, J. H., Shin, Y. K., Han, J. H., Lee, J. H., Lee, S. P., Zhang, J., Einen, M., & Mignot, E. (2006). A study of the diagnostic utility of HLA typing, CSF hypocretin-1 measurements, and MSLT testing for the diagnosis of narcolepsy in 163 Korean patients with unexplained excessive daytime sleepiness. Sleep, 29(11), 1429–1438.

Imbach, L. L., Valko, P. O., Li, T., Maric, A., Symeonidou, E. R., Stover, J. F., Bassetti, C. L., Mica, L., Werth, E., & Baumann, C. R. (2015). Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial. Brain : a journal of neurology, 138(Pt 3), 726–735.

Klerman, E. B., & Dijk, D. J. (2008). Age-related reduction in the maximal capacity for sleep--implications for insomnia. Current biology : CB, 18(15), 1118–1123.

Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al. Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts [published online ahead of print, 2020 Mar 23]. Sleep Med Rev. 2020;52:101306.

Marti, I., Valko, P. O., Khatami, R., Bassetti, C. L., & Baumann, C. R. (2009). Multiple sleep latency measures in narcolepsy and behaviourally induced insufficient sleep syndrome. Sleep medicine, 10(10), 1146–1150.

Mignot, E., Lin, L., Finn, L., Lopes, C., Pluff, K., Sundstrom, M. L., & Young, T. (2006). Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. Brain : a journal of neurology, 129(Pt 6), 1609–1623.

Ruoff, C., Pizza, F., Trotti, L. M., Sonka, K., Vandi, S., Cheung, J., Pinto, S., Einen, M., Simakajornboon, N., Han, F., Peppard, P., Nevsimalova, S., Plazzi, G., Rye, D., & Mignot, E. (2018). The MSLT is Repeatable in Narcolepsy Type 1 But Not Narcolepsy Type 2: A Retrospective Patient Study. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine, 14(1), 65–74.

Singh, M., Drake, C. L., & Roth, T. (2006). The prevalence of multiple sleep-onset REM periods in a population-based sample. Sleep, 29(7), 890–895.

Trotti, L. M., Staab, B. A., & Rye, D. B. (2013). Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine, 9(8), 789–795.

Figure 1. Flowchart illustrating the stepwise process of elimination finally leading to diagnosing 4 patients suffering from excessive daytime sleepiness (EDS) with narcolepsy type 2 (NC2). MSLT: multiple sleep latency test. NC1: narcolepsy type 1.

Table 1. Characteristics of 4 patients with narcolepsy type 2. D.O.: Disease onset (age, years). Regular: regular rest-activity rhythm, without signs of shift work syndrome or circadian disorders. SOREM: sleep onset REM periods. MSLT: multiple sleep latency test. MSL: mean sleep latency. W>N1>R naps: no of MSLT naps with the sleep stage sequence WAKE→NREM1→REM. TIB: time in bed. WD-WE: difference in TBI between weekdays and weekends.

	Demographics			Actigraphy			PSG	MSLT			Serum
No	Sex	Age	D.O.	Regular	Mean TIB	WD-WE	SOREM	MSL	SOREM	W>N1>R naps	HLA-DQBI*0601
1	m	36	18	yes	8.4 hours	1.2 hours	0	3.5 min	2	1	positive
2	m	32	13	yes	7.9 hours	0.9 hours	0	4.0 min	3	0	positive
3	m	74	71	yes	8.6 hours	0.3 hours	1	4.3 min	4	2	positive
4	m	16	14	yes	9.2 hours	2.6 hours	0	4.1 min	3	2	positive